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Neutrophil-to-lymphocyte ratio as a predictor of progression in patients with early-stage cervical cancer

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ABSTRACT

Aims: The neutrophil-to-lymphocyte ratio (NLR) has shown promise as a prognostic marker in various cancers, but its role in early-stage cervical cancer is not well defined. This study evaluates the association between pre-treatment NLR and progression risk in patients with early-stage cervical cancer.

Methods: This retrospective study included 220 patients with stage I and II cervical cancer treated from 2010 to 2024. Patients with prior treatment, infection at diagnosis, or hematological diseases were excluded. Pre-treatment NLR was calculated from blood counts taken within a week before treatment. Primary outcome was progression-free survival (PFS). Cox regression analyses identified prognostic factors.

Results: The median follow-up was 46 months (range, 1-120). Disease progression occurred in 17.3% of patients, and 15% died. The 5-year overall survival and PFS rates were 84.8% (95% CI: 79.3-90.3) and 77.7% (95% CI: 71.4-84), respectively. Univariate analysis identified non-squamous cell carcinoma (non-SCC) histology, tumor size >4 cm, and elevated NLR as significant factors affecting PFS. Multivariate analysis confirmed non-SCC histology (HR: 3.2, p=0.002), tumor size >4 cm (HR: 2.3, p=0.007), and elevated NLR (HR: 1.1, p=0.041) as independent PFS risk factors. Higher NLR correlated with larger tumor size.

Conclusion: Elevated pre-treatment NLR independently predicts disease progression in early-stage cervical cancer. Incorporating NLR into risk stratification could enhance prognostic assessments and guide personalized treatments. Larger prospective studies are needed for validation.

Keywords: Neutrophil-to-lymphocyte ratio, cervical cancer, progression-free survival.

INTRODUCTION

Cervical cancer remains a significant contributor to morbidity and mortality among women globally, especially in developing nations where access to screening and treatment is often limited.[1,2] Despite advancements in diagnostic modalities and therapeutic interventions, a subset of patients diagnosed with early-stage cervical cancer experience disease progression or recurrence.[3-5] Thus, there is an urgent need to identify reliable prognostic markers that can assist in risk stratification and inform personalized therapeutic strategies.

In recent years, the host inflammatory response has garnered substantial attention in the oncology landscape as a potential determinant of cancer progression and treatment outcome.[6,7] The neutrophil-to-lymphocyte ratio (NLR), a simple and easily accessible marker reflecting the balance between pro-inflammatory neutrophils and anti-tumoral lymphocytes, has emerged as a promising prognostic indicator in various malignancies.[8,9] Elevated NLR has been associated with adverse clinical outcomes, including advanced disease stage, metastasis, and reduced survival, across a spectrum of cancer types.[10] While the prognostic significance of NLR has been extensively explored in several solid tumors, its role in early-stage cervical cancer remains relatively underexplored and inconclusive. This retrospective study aims to assess the association between pre-treatment NLR and progression risk in patients diagnosed with early-stage cervical cancer. By elucidating the prognostic value of NLR within this specific cohort, we endeavor to augment the current body of evidence and offer insights into refining risk stratification algorithms and optimizing therapeutic decision-making for the management of early-stage cervical cancer.

METHODS

The study was carried out with the permission of Hacettepe University Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.03.2024, Decision No: 2024/06-15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Informed consent was waived due to the retrospective nature of the study and the use of anonymized data.

The study included a total of 220 patients diagnosed with stage I and stage II cervical cancer according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) classification, who were followed up in our tertiary center between 2010 and 2024. Patients who had received prior treatment for cervical cancer, had an infection at the time of diagnosis, were using corticosteroids, or had concurrent hematological disorders were excluded from the study. Age at diagnosis, Eastern Cooperative Oncology Group- performance status (ECOG-PS), comorbid diseases, histological subtype, FIGO stage, presence of parametrial invasion, the greatest dimension of tumor, pre-treatment blood neutrophil and lymphocyte counts, progression and death data were obtained retrospectively from the hospital electronic database. Patients were treated with surgery, radiotherapy, or concurrent chemoradiotherapy, depending on their stage and disease burden. No one underwent fertility-sparing surgery. The pre-treatment NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained from routine complete blood count tests conducted within one week prior to the initiation of cancer-directed therapy. The primary outcome of interest was progression-free survival (PFS), defined as the duration from initial diagnosis to progression, death from any cause, or the last follow-up visit. Disease progression was determined based on radiological imaging and/or clinical findings. The time from diagnosis to death or last follow-up visit was determined as overall survival (OS). OS defined the time from diagnosis to death from any cause or last follow-up visit. In analyzing the impact on survival outcomes, NLR was assessed as a continuous variable in its pure form. The term 'elevated NLR' refers to high NLR values without specifying any particular cutoff.

Statistical Analysis

All data of the study were analyzed with IBM® SPSS® Statistics 27 and GraphPad Prism 9 software. Descriptive statistics were presented as frequency (percent) or median (min-max). The Mann-Whitney U test was used to compare nonparametric continuous variables between two independent groups. Survival estimates were calculated with the Kaplan-Meier method. Univariate and multivariate analyses of PFS were conducted using the Cox regression method. A 5% type-I error level set to determine statistical significance.

RESULTS

Patient Characteristics

The study included 220 patients with a median age at diagnosis of 56 years (range, 33-84). The ECOG-PS scores were 0 in 143 patients (65%), 1 in 73 patients (33.2%), and 2 in 4 patients (1.8%). The most common comorbidity was hypertension, affecting 32.7% of the patients. Other comorbidities included diabetes mellitus (18.2%), hypothyroidism (2.3%), asthma (2.3%), and various other diseases (7.3%). Histologically, 87.3% of cervical cancer cases were Squamous cell carcinoma (SCC), 6.8% were adenocarcinoma, and 5.9% were other histological subtypes. Regarding 2018 FIGO staging, 38 patients (17.3%) were classified as stage IB, 25 patients (11.4%) as stage IIA, and 157 patients (71.4%) as stage IIB. Parametrial invasion was observed in 157 patients (71.4%), and the largest tumor diameter exceeded 4 cm in 114 patients (51.8%), (Table 1).

Table 1. Patient characteristics (total 220 patients)

Characteristics	Groups	Frequency (%)
Age at diagnosis	<65 years ≥65 years	165 (75) 55 (25)
ECOG-PS	0 1 2	143 (65) 73 (33.2) 4 (1.8)
Comorbid diseases	Hypertension Diabetes mellitus Hypothyroidism Asthma Others	72 (32.7) 40 (18.2) 5 (2.3) 5 (2.3) 16 (7.3)
Histological subtype	Squamous cell carcinoma Adenocarcinoma Others	192 (87.3) 15 (6.8) 13 (5.9)
2018 FIGO stage	IB IIA IIB	38 (17.3) 25 (11.4) 157 (71.4)
Parametrial invasion	Absent Present	63 (28.6) 157 (71.4)
The greatest dimension of tumor	≤4 cm >4 cm	106 (48.2) 114 (51.8)

ECOG-PS: Eastern cooperative oncology group-performance status, FIGO: International federation of gynecology and obstetrics.

Factors Associated with NLR

The median NLR level was 2.73 (range, 0.97-39.4). Possible relationships between patient characteristics and median NLR levels were investigated. No significant relationships were found between median NLR levels and age at diagnosis (≥65 vs. <65 years, p=0.865), ECOG-PS (≥1 vs. 0, p=0.738), presence of comorbid diseases (p=0.084), non-SCC histology (p=0.618), or presence of parametrial invasion (p=0.863). However, the median NLR level was significantly higher in patients with the greatest tumor dimension >4 cm compared to those with the greatest tumor dimension ≤4 cm (3.04 (2.19-4.10) vs. 2.34 (1.74-3.51), p=0.002] (Table 2, Figure 1).

Table 2. Comparison of patient characteristics according to median NLR level

Characteristics	Groups	NLR, median (IQR)	p
Age at diagnosis	<65 years ≥65 years	2.67 (1.98-3.78) 2.93 (1.74-4.15)	0.865
ECOG-PS	0 ≥1	2.64 (1.89-3.88) 2.93 (1.99-3.65)	0.738
Comorbid disease(s)	Absent Present	2.83 (0.08-4.03) 2.67 (1.74-3.43)	0.084
Histological subtype	SCC Others	2.79 (1.94-3.87) 2.54 (1.86-3.50)	0.618
Parametrial invasion	Absent Present	2.57 (1.86-4.00) 2.87 (1.93-3.81)	0.863
The greatest dimension of tumor	≤4 cm >4 cm	2.34 (1.74-3.51) 3.04 (2.19-4.10)	0.002

ECOG-PS: Eastern cooperative oncology group-performance status, IQR: Interquartile range, NLR: Neutrophil-to-lymphocyte ratio, SCC: Squamous cell carcinoma.

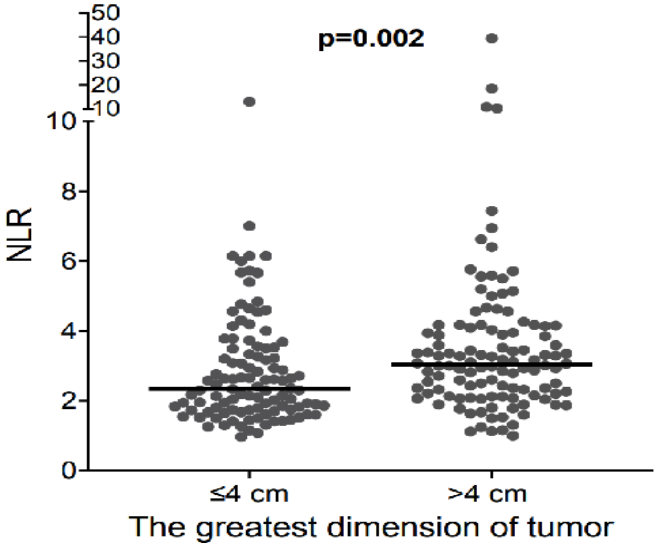

Figure 1. Comparison of pre-treatment median neutrophil-to-lymphocyte ratio (NLR) levels between cases with the greatest dimension of tumor ≤4 cm and those with the dimension >4 cm.

Survival Analysis

During a median follow-up period of 46 months (range, 1-120), 38 patients (17.3%) experienced disease progression, and 33 patients (15%) died. The 5-year PFS and OS rates were 77.7% (95% CI: 71.4-84) and 84.8% (95% CI: 79.3-90.3), respectively. The median PFS and OS times were not reached. In univariate Cox regression analyses, non-SCC histology (HR: 2.7, p=0.003), the greatest tumor dimension >4 cm (HR: 2.3, p=0.006), and NLR level (HR: 1.1, p<0.001) were found to significantly affect PFS. The independent effects of parameters estimated to have a clinical impact on survival were examined by multivariate Cox regression analysis. Examination of the correlation matrix confirmed no significant multicollinearity between the parameters. The final model included age at diagnosis (≥65 vs. <65 years), ECOG-PS (≥1 vs. 0), presence of comorbid diseases, non-SCC histology, presence of parametrial invasion, the greatest tumor dimension (>4 vs. ≤4 cm), and NLR level. Non-SCC histology (HR: 3.2, 95% CI: 1.5-6.8, p=0.002), the greatest tumor dimension >4 cm (HR: 2.3, 95% CI: 1.3-4.2, p=0.007), and NLR level (HR: 1.1, 95% CI: 1.0-1.1, p=0.041) were identified as independent poor prognostic factors for PFS (Figure 2, Table 3).

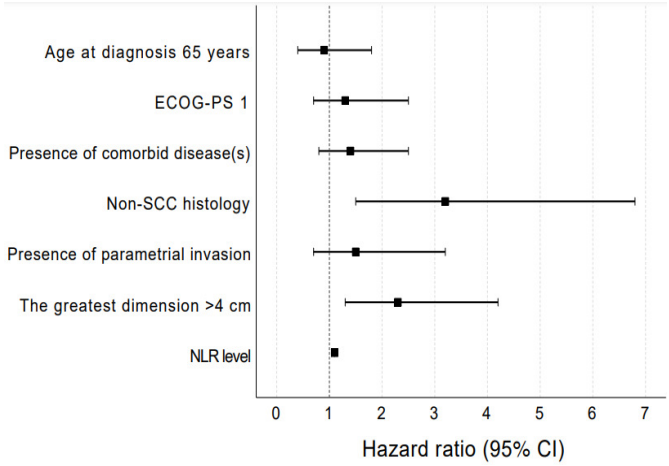

Figure 2. Forest plot depicting risk factors for progression-free survival based on multivariate Cox regression analysis.

Table 3. Risk factors for progression-free survival - Cox regression analysis.

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age at diagnosis ≥65 years	1.3 (0.7-2.3)	0.463	0.9 (0.4-1.8)	0.697
ECOG-PS ≥1	1.3 (0.8-2.3)	0.296	1.3 (0.7-2.5)	0.477
Presence of comorbid disease(s)	1.2 (0.7-2.1)	0.436	1.4 (0.8-2.5)	0.269
Non-SCC histology	2.7 (1.4-5.2)	0.003	3.2 (1.5-6.8)	0.002
Presence of parametrial invasion	1.3 (0.7-2.7)	0.402	1.5 (0.7-3.2)	0.245
The greatest dimension >4 cm	2.3 (1.3-4.1)	0.006	2.3 (1.3-4.2)	0.007
NLR level	1.1 (1.0-1.1)	<0.001	1.1 (1.0-1.1)	0.041

Confidence interval, ECOG-PS: Eastern cooperative oncology group-performance status, HR: Hazard ratio, NLR: Neutrophil-to-lymphocyte ratio, SCC: Squamous cell carcinoma.

We categorized the NLR values into four quartiles: 0-1.93, 1.94-2.73, 2.74-3.83, and ≥3.84, with 55 patients in each group. Analyzing the relationship between these NLR categories and PFS, we observed a 2-year PFS rate of 92.6% (95% CI: 84.6-100.6) in the first group, 87.9% (95% CI: 78.7-97.1) in the second group, 82.4% (95% CI: 72-92.8) in the third group, and 68.9% (95% CI: 56.2-81.6) in the fourth group (p=0.005), (Figure 3). NLR of ≥3.84 was associated with a 2-fold increased risk of progression during follow-up (HR: 2.1, 95% CI: 1.2-3.7, p=0.010).

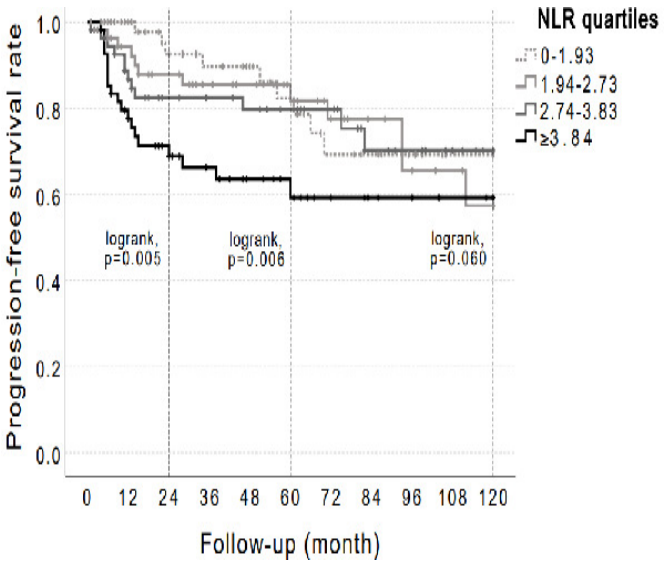

Figure 3. Kaplan-Meier curves for progression-free survival according to neutrophil-to-lymphocyte ratio (NLR) quartiles.

DISCUSSION

This study revealed a significant association between elevated pre-treatment NLR and an increased risk of disease progression, underscoring the prognostic relevance of this easily accessible hematological parameter in the context of cervical cancer. Neutrophils are integral components of the tumor microenvironment and contribute to progression through various mechanisms, including secretion of proliferative factors and suppression of T-lymphocyte activity.[11] The underlying mechanisms driving this association

are multifaceted and likely involve the interplay between the host immune response and tumor microenvironment dynamics.[12,13] Neutrophils can directly interact with tumor cells to enhance their invasive and metastatic potential. Neutrophil-derived proteases, such as matrix metalloproteinases, facilitate extracellular matrix degradation, promoting tumor cell invasion and dissemination to distant sites.[14] Moreover, neutrophils can form heterotypic interactions with tumor cells, leading to the formation of neutrophil-tumor cell aggregates that facilitate tumor cell extravasation and metastatic seeding. Conversely, lymphocytopenia may signify impaired cellular immunity and compromised tumor surveillance, thereby fostering tumor escape mechanisms and disease dissemination.[15]

In a meta-analysis of 14 studies including 6041 cervical cancer patients, higher NLR was associated with worse OS (HR 1.9, 95%CI: 1.4-2.4) and PFS (HR 1.7, 95%CI: 1.3-2.2) compared with lower NLR.[16] In another study including 99 cervical cancer patients receiving definitive chemoradiotherapy, NLR values before, during, and after treatment were found to be related to PFS and OS.[17] Most recently, Du et al.,[18] demonstrated the association of high NLR level with shorter PFS in their study including 203 patients with early-stage cervical cancer. Consistent with prior investigations, our study demonstrates that elevated NLR serves as an independent prognostic factor for disease progression in early-stage cervical cancer.

In the study conducted by Prabowo IPY, et al.,[19] the median NLR level was found to be higher in stage III-IV cervical cancer patients than in stage I-II cases, and a strong positive correlation was revealed between the disease stage and the NLR level (r=0.638). We also observed association between elevated NLR and larger tumor size, underscores the potential role of NLR as a surrogate marker for aggressive tumor behavior. While the precise biological underpinnings linking NLR to tumor aggressiveness warrant further elucidation, our findings support that NLR reflects the disease progression.

From a clinical perspective, the incorporation of pretreatment NLR into risk stratification algorithms holds promise for refining prognostic assessment and guiding personalized therapeutic decision-making in early-stage cervical cancer. Identifying patients at higher risk of disease progression based on NLR status may facilitate tailored treatment approaches, such as intensified surveillance protocols, adjuvant therapies, or enrollment in clinical trials evaluating novel therapeutic agents. Moreover, serial monitoring of NLR dynamics throughout the disease course may offer valuable insights into treatment response and disease trajectory, enabling timely modifications to therapeutic strategies by evolving risk profiles.

Limitations

Nevertheless, several limitations inherent to retrospective studies warrant consideration when interpreting the findings of this investigation. Despite efforts to adjust for potential confounders through multivariate analysis, residual biases and unmeasured variables may have influenced the observed associations. Additionally, the single-center nature of the study and the relatively modest sample size limits the generalizability of the findings and underscore the need for validation in larger, multicenter cohorts. Prospective studies are warranted to elucidate the dynamic interplay between NLR, tumor biology, and clinical outcomes in early-stage cervical cancer.

CONCLUSION

In conclusion, our study provides compelling evidence supporting the prognostic significance of pretreatment NLR in early-stage cervical cancer. Future prospective studies are warranted to validate these findings, elucidate underlying biological mechanisms, and explore the clinical utility of NLR-guided therapeutic algorithms in optimizing patient outcomes in managing early-stage cervical cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of HacettepeUniversity Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.03.2024, Decision No: 2024/06-15)

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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